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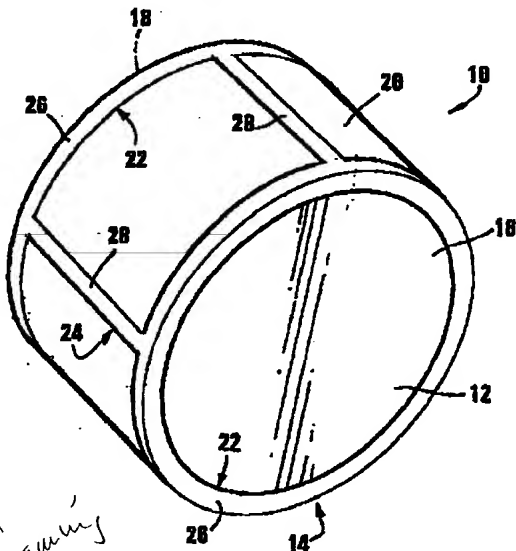
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(54) Title: AN ARTEFACT SUITABLE FOR USE AS A BONE IMPLANT

(57) Abstract

An artefact (10) suitable for use as a bone implant by implantation thereof into a subject at a body site where bone growth is required, comprises a porous body (12) of bioactive material, and a support structure (14) supporting the porous body (12) and acting as a mechanical reinforcement for the bioactive body (12). The support structure (14) is of a material which is less porous than the body (12).



no intermediate layer  
no forming

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AN ARTEFACT SUITABLE FOR USE AS A BONE IMPLANT

THIS INVENTION relates to an artefact suitable for use as a bone implant by implantation thereof into a subject at a body site where bone growth is required. It relates also to a method of making such an artefact.

5 According to a first aspect of the invention, there is provided an artefact suitable for use as a bone implant by implantation thereof into a subject at a body site where bone growth is required, the artefact comprising a porous body of bioactive material, and a support structure  
10 supporting the porous body and acting as a mechanical reinforcement for the bioactive body, with the support structure being of a material which is less porous than the body.

The porous bioactive body or biomaterial thus, in use,  
15 permits bone growth into its porous spaces, thereby to secure its incorporation into and osteointegration with the surrounding viable bone at the margins of a bone defect at the site where the artefact is implanted. The bioactive body may thus be osteoconductive, ie permitting bone growth  
20 into its porous spaces when it is in direct contact with viable bone, and/or osteoinductive, ie permitting bone

growth into its porous spaces independently of the presence of viable bone in contact with the artefact.

The pores should, for good osteoinductive or osteoconductive capability, comprise from 40 to 80% of the total volume of the bioactive body. At least some of the pores must be connected to the outer or external surface of the body. Thus, between 40 and 100% of the pores may be connected to the external body surface. This connection may be direct, eg by way of an aperture, channel, pathway or the like, from a pore to the surface, and/or even a pore integrated with the surface, eg being in the form of an indentation or concavity in the surface. Instead, or additionally, the connection of the pores to the external surface may be indirect, eg by a particular pore being connected to another pore which is connected directly to the external surface as described, or connected to a series or sequence of connected pores, at least one of which is directly connected to the surface, as described.

The pores may be of substantially spherical shape, and may have diameters or cross-sectional dimensions in the range 200-3000 micron.

The bioactive material of the body may be sintered bioactive ceramic or glass material. In particular, it may be a calcium phosphate-based ceramic material such as hydroxyl-apatite or tricalcium phosphate.

The support structure may comprise at least two interconnected support components or parts. The components or parts may at least partially surround or enclose the body and/or may be at least partially embedded in the body.

For example, the body may be of more or less cylindrical or disc form, with the support structure comprising a pair of rings abutting the respective ends of the body and a plurality of circumferentially spaced connecting members connecting the rings and extending alongside or through the body, with the rings and connecting members thus constituting interconnected support components of the support structure.

The support structure is, as stated, less porous than the body. Thus, when pores are present in the material of the support structure, the proportion of pores will be less than the proportion of pores in the body. Typically, when the body has a porosity of 40-80% as hereinbefore described, the pores in the support structure will comprise 20% or less of the total volume of the support structure. The support structure may even be of solid material, ie contain substantially no pores.

The material of the support structure may also be bioactive, and may then be the same as that of the body, eg it may be hydroxylapatite. Instead, however, the material of the support structure may be resorbable, such as tricalcium phosphate; it may be bioinert such as alumina; or it may be pliable such as high density polyethylene.

According to a second aspect of the invention, there is provided a method of making an artefact suitable for use as a bone implant by implantation thereof into a subject at a body site where bone growth is required, which method comprises

compressing a precursor mixture comprising a bioactive material in particulate form and heat-decomposable

particles of a heat-decomposable substance, to form a green body, with the green body having spaces or recesses for a support structure ;

filling the spaces or recesses with a support structure material in particulate form, to form a non-consolidated green body;

compressing the non-consolidated green body to form a consolidated green body;

heating the consolidated green body, to permit controlled decomposition of the heat-decomposable particles and to sinter the body and the support structure, thereby to form a unitary artefact comprising a porous bioactive body and a less porous support structure supporting the porous bioactive body and acting as a mechanical reinforcement for the porous bioactive body.

As hereinbefore described, both the bioactive material and the support structure material may be hydroxylapatite, and the material may initially be in powder form.

The heat decomposable particles may be stearic acid spheres, typically having a diameter between 600 and 1000 micron, with pores slightly smaller than this subsequently being formed in the body. The mass ratio of powdered hydroxylapatite to stearic acid spheres will be selected to give a desired porosity to the body, and typically is about 2:3 by mass, to give a body porosity of about 55% to 70%, typically about 65%.

The initial compressing may be effected by uniaxially pressing the precursor mixture into the form of a solid cylinder or disc having circumferential recesses in its ends and circumferentially spaced recesses in its side, or

passageways through it, interconnecting the circumferential recesses. This pressing may be effected at low pressure eg at about 5 MPa.

5 The subsequent compressing of the non-consolidated green body may also be in the form of uniaxial pressing, which may be at a higher pressure eg at about 50 MPa.

10 The heating or firing may initially be effected at a first predetermined rate, eg at about 25°C/hour, up to a first predetermined temperature, eg about 100°C, to permit controlled melting and decomposition of the stearic acid spheres; thereafter at a second predetermined rate, eg about 50°C/hour, up to a second predetermined temperature, eg to about 400°C; and then at a third predetermined rate, eg about 100°C/hour, up to a third predetermined temperature, eg about 1260°C, with this temperature being maintained for a predetermined soak time, eg about 4 hours, to sinter the body and the support structure. The artefact is then allowed to cool to room temperature, while keeping it in the furnace. This cooling is typically effected for about 8 hours.

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The invention will now be described, by way of example, with reference to the accompanying drawing which shows a three-dimensional view of an artefact for use as a bone implant by implantation thereof into a subject at a body site where bone growth is required, according to the invention.

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In the drawing, reference numeral 10 generally indicates the artefact.

The artefact 10 includes a solid cylindrical or disc like porous hydroxylapatite body 12, and a less porous support structure 14 also of hydroxylapatite supporting the body 12.

5 The body 12 thus comprises circular planar ends 16, 18 and a cylindrical outer surface 20 between the ends 16, 18. Circumferential recesses 22 are provided in the ends 16, 18, with circumferentially spaced grooves or recesses 24 provided in the surface 20 and connecting the recesses 22.

10 The body 12 typically has a porosity of 40-80%, based on the total volume of the body, with the size of the pores, which are substantially spherical, being in the range 600-1000 microns. 40-100% of the pores are connected to the internal surfaces of the body 12, either directly or  
15 indirectly as hereinbefore described.

The support structure 14 comprises rings 26 of hydroxylapatite located in the recesses 22 and integrally bonded or fused with the body 12 by sintering. The support structure 14 also comprises support members in the form of  
20 pillars or pins 28 extending along the recesses or passageways 24 and connecting the rings 26. The pillars or pins 28 are also integrally sintered with the body 12 and the rings 26.

The support structure 14 is of substantially solid  
25 hydroxylapatite, ie contains substantially no pores.

The artefact 10 can be formed by initially preparing a precursor mixture. The precursor mixture comprises hydroxylapatite powder mixed with 600-1000 micron diameters



stearic acid spheres in a mass ratio of 2:3. A cylindrical or disc-like compact is uniaxially pressed at a low pressure of 5 MPa from the precursor mixture, using a die and pistons (not shown) with inserts (also not shown) in such a way that the recesses 22 and passageways 24 are formed therein. The pistons and inserts are removed from the die, and the recesses and passageways filled with hydroxylapatite powder. The resultant non-consolidated green body or assembly is then uniaxially pressed at a higher pressure of 50 MPa, to form a well consolidated green body. The green body is fired in a furnace at an initial heating rate of 50°C/hour up to 500°C to allow controlled melting and decomposition of the stearic acid spheres, thereby forming the voids in the body. Thereafter, the artefact is further heated at a heating rate of 100°C/hour up to 1250°C, and maintained at this temperature for a soak time of 4 hours, to sinter the body and the support structure 14, and to fuse them together. The resultant artefact thus has its support structure 14 intimately bound to the body 12.

In the artefact 10, the support structure 14 thus provides a mechanical reinforcement for the body 12, thereby rendering it suitable for load bearing applications. More specifically, the support structure 14 imparts strength to the artefact 10, while the porous body 12, in use, encourages bone generation and bone growth, either by osteoconductivity or osteoinductivity.

Generally, in bone substitutes or bone implants of hydroxylapatite or the like, a high degree of porosity, ie a high percentages of pores in the porous body, as well as a large number of pores, ie pores of as small a size as is

feasible so as to have a large number of small pores rather than a small number of large pores, are desirable for good bone growth. However, as the number of pores and the porosity increases, the strength of the implant decreases, so that biomaterial comprising only porous hydroxylapatite, normally cannot be used in load bearing applications. In contrast, with the artefact 10, which incorporates the support structure 14 having either no pores or a lower porosity and a small number of pores, the required strength for load bearing application is achieved.

In the artefact 10, the spacing between the pores in the body 12 can also be maintained at as small a distance as is practically feasible, eg the pores can coalesce into each other rather than having them interconnected by relatively small channels or passageways which also inhibits bone ingrowth.

The Applicant thus believes that the artefact in accordance with the invention will give good results when used as a bone substitute in load bearing applications due to

- its open fully connected approximately spherical pores of 200-3000 micron diameter
- its high volume fraction of such open porosity, which will permit significant bone ingrowth
- the reinforcement provided by the support structure 14 which provides adequate mechanical property
- the absence of foreign intrusions or second phase materials which could inhibit bone ingrowth; however, if desired, the support structure can be of a second phase or different material
- is manufactured of hydroxylapatite which has intrinsic osteoinductive capability.

Additional advantages which the artefact of the present provides over known bone implants include:

- it is possible to concentrate the solid support structure in specific regions of the artefact, while  
5 retaining a large volume fraction of suitable porosity in the remainder of the artefact, ie in the body 12
- the solid ceramic support structure 14 can, as described, have the same chemical composition as the porous bioactive ceramic body or structure 12, thereby  
10 minimizing the possibility of unwanted interreactions between the support structure 14 and the body 12
- if desired, however, the solid ceramic support structure 14 can have a different chemical composition to that of the porous bioactive ceramic body 12 eg it  
15 can have a closely related but resorbable composition, to allow gradual resorption of the solid support during bone ingrowth in the porous body 12; the solid support structure 14 thus provides mechanical support and need not necessarily possess bioactive properties
- 20 - the extent of support and directional properties of the support structure 14 can be readily modified or optimised for particular applications
- during manufacture, it is possible to extend the solid support structure by protrusions such as pins or end  
25 caps which can be useful in locating or fixing the position of the implant relative to that of the natural bone or tissue at the defect
- it is possible to employ minimal mechanical reinforcement, for example to prevent edge chipping or  
30 fracture which occur due to bending of porous ceramics, in non-load bearing applications.

**CLAIMS:**

1. An artefact suitable for use as a bone implant by implantation thereof into a subject at a body site where bone growth is required, the artefact comprising a porous  
5 body of bioactive material, and a support structure supporting the porous body and acting as a mechanical reinforcement for the bioactive body, with the support structure being of a material which is less porous than the body.
- 10 2. An artefact according to Claim 1, wherein the porous body is osteoconductive and osteoinductive.
3. An artefact according to Claim 1 or Claim 2, wherein the pores of the body comprise from 40% to 80% of the total volume of the body.
- 15 4. An artefact according to any one of Claims 1 to 3 inclusive, wherein from 40% to 100% of the pores of the body are connected to the outer or external surface of the body.
- 20 5. An artefact according to Claim 4, wherein the connection of the pores of the body to the external surface of the body is directly by way of apertures, channels or pathways from the pores to the body surface and/or by way of pores integrated with the external body surface by being in the form of indentations or concavities in the external  
25 body surface.

6. An artefact according to Claim 4, wherein the connection of the pores of the body to the external surface of the body is indirectly by means of pores connected to other pores which are connected directly to the external surface of the body and/or by means of pores connected to a series or sequence of connected pores, at least one of which is directly connected to the external surface.

7. An artefact according to any one of Claims 1 to 6 inclusive, wherein the pores are of substantially spherical shape, and have diameters in the range 200-3000 microns.

8. An artefact according to any one of Claims 1 to 7 inclusive, wherein the bioactive material of the body is hydroxylapatite or tricalcium phosphate.

9. An artefact according to any one of Claims 1 to 8 inclusive, wherein the support structure comprises at least two interconnected support components or parts which at least partially surround or enclose the body and/or are at least partially embedded in the body.

10. An artefact according to Claim 9, wherein the body is of more or less cylindrical or disc form, with the support structure comprising a pair of rings abutting the respective ends of the body and a plurality of circumferentially spaced connecting members connecting the rings and extending alongside or through the body, with the rings and connecting members thus constituting interconnected support components of the support structure.

11. An artefact according to any one of Claims 1 to 10 inclusive, wherein pores are present in the material of the support structure, with the proportion of the pores in the material of the support structure being less than the proportion of the pores in the body.

12. An artefact according to any one of Claims 1 to 10 inclusive, wherein the material of the support structure is solid and thus contains substantially no pores.

13. A method of making an artefact suitable for use as a bone implant by implantation thereof into a subject at a body site where bone growth is required, which method comprises

compressing a precursor mixture comprising a bioactive material in particulate form and heat-decomposable particles of a heat-decomposable substance, to form a green body, with the green body having spaces or recesses for a support structure;

Filling the spaces or recesses with a support structure material in particulate form, to form a non-consolidated green body;

compressing the non-consolidated green body to form a consolidated green body;

heating the consolidated green body, to permit controlled decomposition of the heat-decomposable particles and to sinter the body and the support structure, thereby to form a unitary artefact comprising a porous bioactive body and a less porous support structure supporting the porous bioactive body and acting as a mechanical reinforcement for the porous bioactive body.

14. A method according to Claim 13, wherein both the bioactive material and the support structure material are hydroxylapatite, which is initially in powder form.

5 15. A method according to Claim 14, wherein the heat decomposable particles are stearic acid spheres, having a diameter between 500 and 1000 microns, with pores slightly smaller than this subsequently being formed in the body.

10 16. A method according to Claim 15, wherein the mass ratio of powdered hydroxylapatite to stearic acid spheres is about 2:3 by mass, to give a body porosity of about 55% to 70%.

15 17. A method according to Claim 15 or Claim 16, wherein the initial compressing is effected by uniaxially pressing the precursor mixture into the form of a solid cylinder or disc having circumferential recesses in its ends and circumferentially spaced recesses in its side and/or passageways through it and interconnecting the circumferential recesses, with the pressing being effected at a low pressure of about 5 MPa.

20 18. A method according to Claim 17, wherein the subsequent compressing of the non-consolidated green body is also in the form of uniaxial pressing, which is at a higher pressure of about 50 MPa.

25 19. A method according to any one of Claims 15 to 18 inclusive, wherein the heating or firing of the green body is initially effected at a first rate, up to a first temperature, to permit controlled melting and decomposition of the stearic acid spheres; thereafter at a second rate,

up to a second temperature, and then at a third rate, up to a third temperature, with the third temperature being maintained for a s ak time, to effect the sintering of the body and the support structure, whereafter the artefact is allowed to cool to room temperature.

20. A novel artefact, substantially as described and illustrated herein.

21. A novel method of making an artefact, substantially as described and illustrated herein.





# INTERNATIONAL SEARCH REPORT

Internat. Application No

PCT/EP 98/01218

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61F2/28 A61L27/00 C04B35/00 C04B38/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61F C04B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 44 09 836 A (DRAENERT) 28 September 1995	1-3, 8-10, 12
Y	see abstract; claims; figures 6-9	4-7
Y	US 5 531 794 A (TAKAGI) 2 July 1996	4-7
A	see the whole document	8
Y	EP 0 398 497 A (UNITED STATES SURGICAL CORPORATION) 22 November 1990 see the whole document	13
Y	EP 0 107 476 A (CALCITEK) 2 May 1984 see the whole document	13
A	US 5 211 664 A (TEPIC) 18 May 1993 see the whole document	1, 10
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

3 July 1998

Date of mailing of the international search report

24. 07. 98

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# INTERNATIONAL SEARCH REPORT

Internatic Application No  
PCT/EP 98/01218

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 28117 A (BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM) 19 September 1996 see the whole document ---	10
A	DE 94 13 778 U (SCHÄFER MICOMED) 4 January 1996 see figures 1,2 ---	10
A	DE 24 26 814 A (U.S. ATOMIC ENERGY COMMISSION) 9 January 1975 see the whole document ---	10,13
A	EP 0 719 529 A (KYOCERA CORPORATION) 3 July 1996 see the whole document ---	13
A	EP 0 631 763 A (SULZER MEDIZINALTECHNIK) 4 January 1995 see the whole document ---	13
A	US 5 549 123 A (OKUYAMA) 27 August 1996 see the whole document ---	13
A	DE 35 31 144 A (TDK CORPORATION) 27 March 1986 see the whole document ---	13
A	US 5 296 180 A (HAYES) 22 March 1994 see the whole document ---	13
A	US 5 266 248 A (OHTSUKA) 30 November 1993 see the whole document ---	13
A	US 5 152 791 A (HAKAMATSUKA) 6 October 1992 ---	
A	US 5 290 494 A (COOMBES) 1 March 1994 -----	

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP 98/01218

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☒ Claims Nos.: 20,21  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
Claims relying on references to the description or drawings: see PCT-Rule 6.2a
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
  
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Internatio. Application No

PCT/EP 98/01218

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 4409836 A	28-09-1995	WO 9525483 A	28-09-1995
US 5531794 A	02-07-1996	JP 7124241 A	16-05-1995
EP 398497 A	22-11-1990	US 5037445 A	06-08-1991
		CA 2013883 A,C	14-10-1990
		DE 69010764 D	25-08-1994
		DE 69010764 T	22-12-1994
EP 107476 A	02-05-1984	JP 59095041 A	31-05-1984
US 5211664 A	18-05-1993	DE 69208350 D	28-03-1996
		DE 69208350 T	14-08-1996
		EP 0551611 A	21-07-1993
WO 9628117 A	19-09-1996	US 5492697 A	20-02-1996
		AU 4757496 A	02-10-1996
DE 9413778 U	04-01-1996	DE 4432033 A	29-02-1996
DE 2426814 A	09-01-1975	US 4070514 A	24-01-1978
		CA 1042165 A	14-11-1978
		CH 574735 A	30-04-1976
		GB 1467887 A	23-03-1977
EP 719529 A	03-07-1996	JP 8173463 A	09-07-1996
EP 631763 A	04-01-1995	AT 150283 T	15-04-1997
		DE 59305884 D	24-04-1997
		US 5665119 A	09-09-1997
US 5549123 A	27-08-1996	JP 7194688 A	01-08-1995
DE 3531144 A	27-03-1986	JP 1950959 C	10-07-1995
		JP 61079462 A	23-04-1986
		JP 61079463 A	23-04-1986
		JP 1771191 C	30-06-1993
		JP 4011215 B	27-02-1992
		JP 61079464 A	23-04-1986
		US 4629464 A	16-12-1986

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 98/01218

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5296180 A	22-03-1994	US 5458837 A US 5298205 A	17-10-1995 29-03-1994
US 5266248 A	30-11-1993	US 5728395 A	17-03-1998
US 5152791 A	06-10-1992	JP 3178652 A	02-08-1991
US 5290494 A	01-03-1994	US 5397572 A US 5492697 A	14-03-1995 20-02-1996